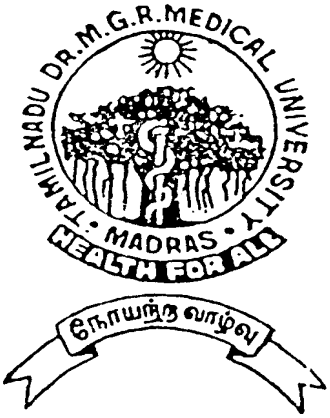
IMPACT OF PYRAZINAMIDE REGIMEN ON SERUM URIC ACID LEVELS IN TB PATIENTS

DISSERTATION SUBMITTED FOR

THE DEGREE OF DOCTOR OF MEDICINE

BRANCH I GENERAL MEDICINE

MARCH – 2009



THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY

CHENNAI – TAMILNADU

CERTIFICATE

This is to certify that the dissertation titled **"Impact of Pyrazinamide regimen on Serum Uric Acid levels in TB patients"** submitted by **Dr.R. Mathan kumar** to the Faculty of Medicine, The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of M.D. Degree (Medicine) is a bonafide research work carried out by him under our direct supervision and guidance.

Dr. Moses K. Daniel M.D.

Professor of Medicine,

Department of Medicine,

Madurai Medical College,

Madurai.

Dr. Iyyappan M.D.

Professor and Head of the Department

Department of Medicine,

Madurai Medical College,

Madurai.

DECLARATION

I. ***Dr. Mathan kumar,*** *solemnly declare that the dissertation titled* ***"Impact of Pyrazinamide regimen on serum uric acid levels in TB patients"*** *has been prepared by me.*

This is submitted to the ***Tamilnadu Dr. M.G.R. Medical University****, Chennai in partial fulfillment of the rules and regulations for the M.D. Degree Examination in General Medicine.*

Place : Madurai

Date : ***Dr. Mathan kumar***

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CONTENTS

INTRODUCTION

Recently increased importance is given to chemotheraphy in the treatment of tuberculosis. This has given great relief to the patients suffering from this disease.

But at the same time, the multidose therapy has resulted in enhanced toxity and other drug reactions. Hence a better understanding of the scientific principles of the phenomenon of drug reaction through various studies has become essential to bring better results in treatment of tuberculosis.

Pyrazinamide was formerly a reserve regimen drug used for the treatment of patients who had failed with primary chemotherapy. Today, Pyrazinamide is at the fore front of the chemotherapeutic armamentorium along with Rifampicin and INH as one of the pillars of Short Course Chemotheraphy. A not infrequent reaction to pyrazinamide is hyperuricemia and arthralgia (Hong Kong / BMRC study 1976, Horsfall 1979, Sharma and Jain, Lung India 1983) which is probably due to inhibition of renal excretion of uric acid. However the exact mechanism of arthralgia is yet to be established on firmer grounds.

The current study was undertaken to determine the incidence of hyperuricemia and arthralgia in regimens containing pyrazinamide.

AIM OF THE STUDY

1. To study incidence of hyperuricemia in patients receiving, anti tuberculosis therapy containing pyrazinamide.

2. To evaluate the incidence arthralgia in the above regimen.

3. To study the relationship between age, sex and drug regimen and incidence of hyperuricemia and arthralgia.

REVIEW OF LITERATURE

Metabolism and Pathological conditions of uric Acid

The end product of purine metabolism in humans is urate, In most of the mammals it is further broken down into the soluble compound, allantoin, and it is the poor solubility of urates which makes man prone to clinical gout and renal damage by urate. The purines adenine and guanine are constituents of both types of nucleic acid (DNA and RNA). The purines used by the body for nucleic acid synthesis may be derived from two sources.

1. Breakdown of ingested nucleic acids (mainly in meat).
2. May be synthesised in the body from small molecules dnovo.

Synthesis of Purines

There are four steps in which synthesis of purine can be considered.

In the first step of purine synthesis : condensation of pyrophosphate with phosphoribose to form phosphoribosyl pyrophosphate (PRPP).

In the second step, amino group of glutamine is incorporated into the ribose phosphate molecule and pyrophosphate is released. Amidiphosphoribosyl tranferase catalyses this rate-limiting or controlling step

in purine synthesis. It is subject to feedback inhibition from increased levels of purine nucleotides. Thus the rate of synthesis is slowed when its products increase. This step may be at fault in primary gout.

In the Third Step, the glycine molecule is added to phosphoribosylamine.

After many complex steps purine ribonucleotides (purine ribose phosphates) are formed and as has already been stated, the level of these controls (Second step). Ribose phosphate is split off, therapy releasing the purines.

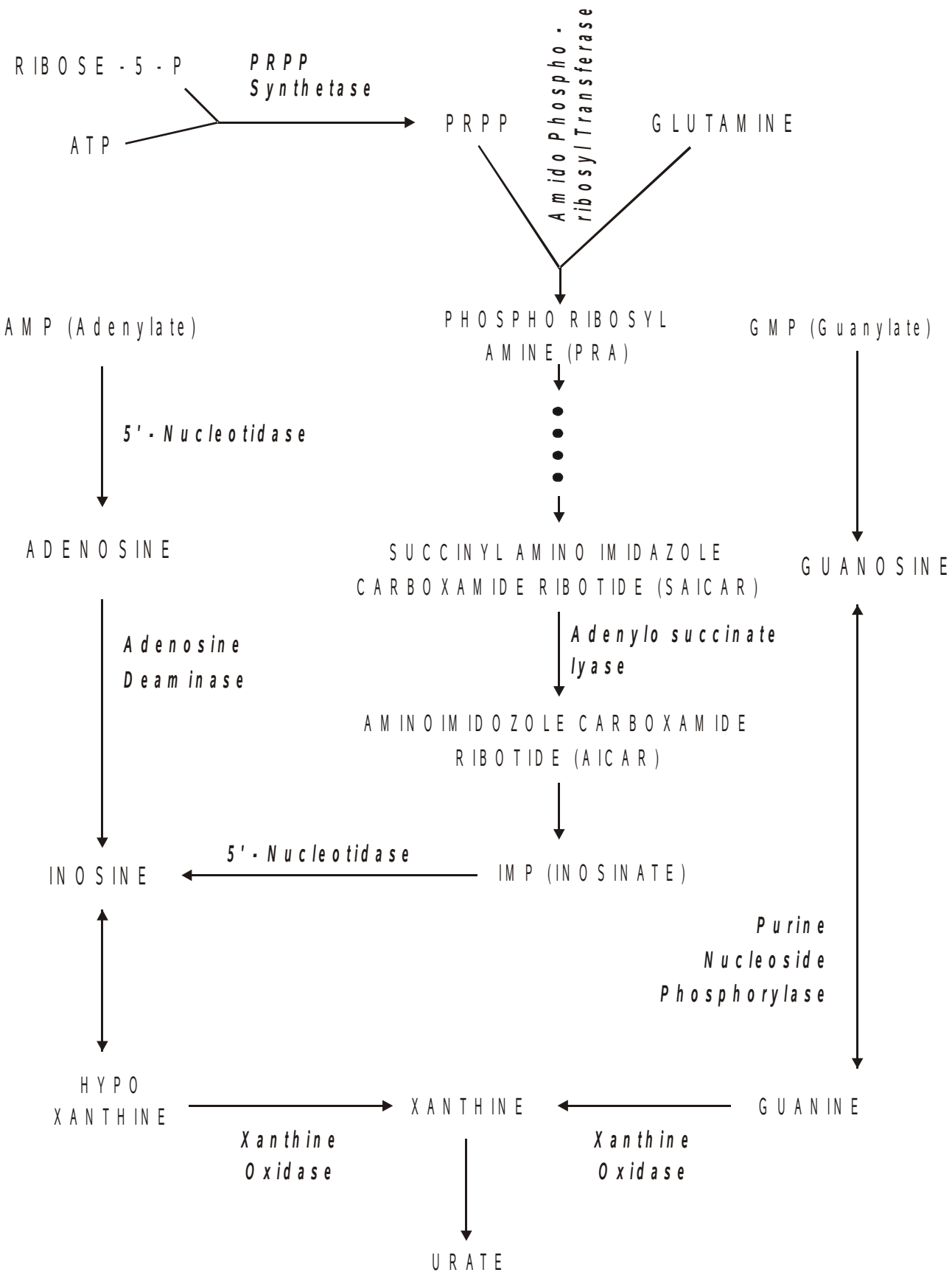
Fate of Purines

Purines synthesised in the body, those derived from the diet and those liberated by endogenous breakdown of nucleic acids may follow one of the two pathways : they may be synthesised into new nucleic acid; or be oxidized to urate.

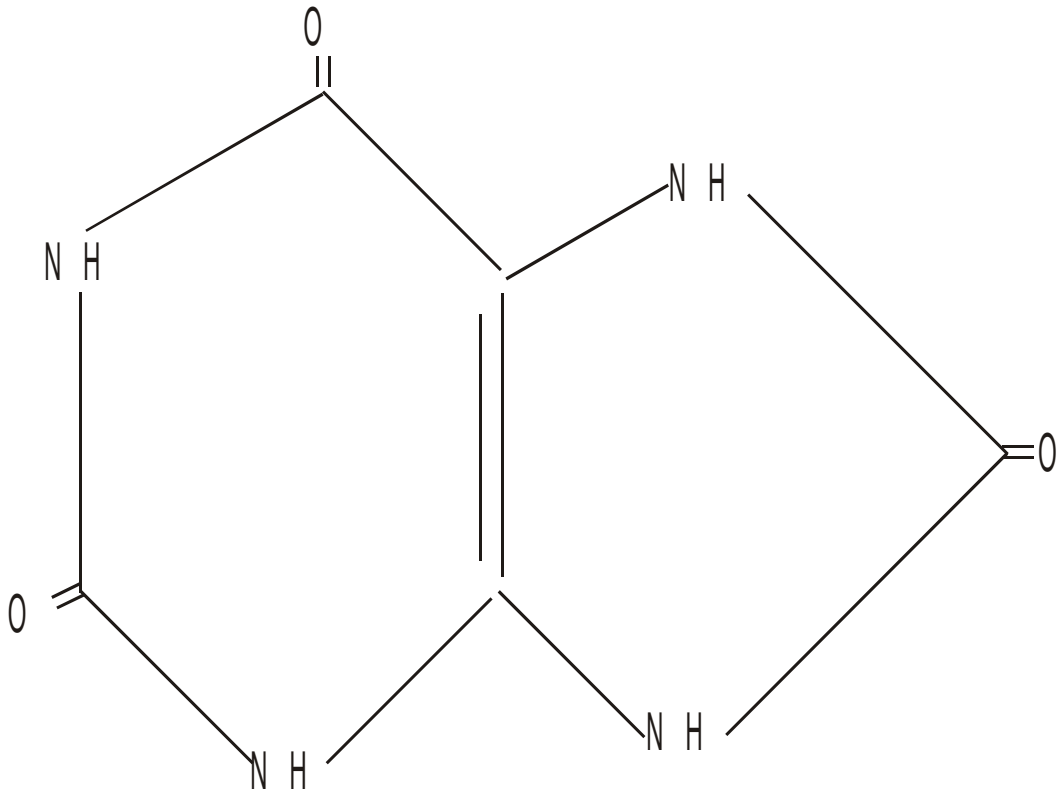
Formation of urate from purines

As shown in the figure, some of adenine is oxidized to hypoxanthine, which is further oxidized to xanthine. Guanine can also form xanthine. Xanthine, in turn is oxidized to form urate. The oxidation of both hypoxanthine and xanthine is catalyzed by the liver enzyme xanthine oxidase. Thus the formation of urate from purines depends on xanthine oxidase activity, a fact of importance in the treatment of gout.

PURINE METABOLISM



STRUCTURE OF URIC ACID



Reutilization of purines

Some xanthine, hypoxanthine and guanine can be resynthesised to purine nucleotides by pathways involving, amongst other enzymes, Hypoxanthine – Guanine Phosphoribosyl Transferase (HGPRT) and Adenine Phosphoribosyl Transferase (APRT).

Excretion of urate

75 percent of the urate leaving the body is excreted in the urine and 25 percent passes into the intestine, where it is broken down by intestinal bacterial (uricolysis). The urate filtered at the renal glomerulus is probably completely reabsorbed in the tubules and the urinary urate is derived from active tubular secretion : urinary excretion may be enhanced by various drugs used in the treatment of gout.

Renal excretion of urate is inhibited by such organic acids as lactic and oxacids.

Uric Acid is the final breakdown product of purine degradation in humans. Serum urate concentrations vary with age and sex. Most children have serum urate concentrations of 3 – 4mg/dl. Levels begin to rise at puberty in males but remain low in females until menopause. Although the cause of this sex variation is unknown, it is in part due to higher functional excretion

of urate in female and is attributable to hormonal influence, Mean serum urate values for men and premenopausal women are 6.8 and 6.8 mg/dl respectively. After menopause, values for women approximate those of men. Adult concentrations rise steadily over the time, vary with height, body weight, blood pressure, renal function and alcohol intake.

Causes of hyperuricemia

It could be due to increased production of uric acid / decreased excretion of Uric Acid or a combination of both.

CLASSIFICATION OF HYPERURICEMIA

Urate over Production

Primary idiopathic HPRT deficiency

PRPP synthetase over activity

Hemolytic proceses

Lymphoproliferative diseases

Polycythemia vera

Psoriasis

Paget's disease

Glycogenosis III,

Glycogenosis V,

and Glycogenosis VII,

Rhabdomyolysis

Exercise

Alcohol

Obesity

Purine-rich diet

Decreased Uric Acid Excretion

Primary idiopathic

Renal insufficiency

Polycystic kidney disease

Diabetes insipidus

Hypertension

Acidosis

- Lactic acidosis
- Diabetic Ketoacidosis

Starvation ketosis

Berylliosis

Sarcoidosis

Lead intoxication

Hyperparathyroidism

Hypothyroidism

Toxemia of pregnancy

Bartters Syndrome

Down syndrome

Drug ingestion

Salicylates (> 2 g/d)

Decreased Uric Acid Excretion

Diuretics

Alcohol

Levodopa

Ethambutol

Pyrazinamide

Cyclosporine

Combined Mechanism

Glucose – 6 phosphatase Deficiency

Fructose – 1 – phosphate – aldolase deficiency

Alcohol

Shock

Complications of hyperuricemia

Asymptomatic hyperuricemia can lead to Acute Gouty arthritis and

chronic or tophaceous gout. Nephrolithiasis can occur before or after first attack of gouty arthritis.

Gout

The term is used to describe a number of disorders in which crystals of monosodium urate monohydrate derived from hyperuricemic body fluids give rise to inflammatory arthritis, tenosynovitis, bursitis or cellulitis, tophaceous deposits, urolithiasis and renal disease. Hyperuricemia is a necessary but not a sufficient pre requisite for clinical manifestation of gout.

Clinical Features

Acute Gout

The metatarsophalangeal joint of great toe is the site of first attack of acute gouty arthritis in 70% of patients; the wrist, the ankle, the knee, the small joints of the feet and hand the elbow follow in decreasing order of frequency. The affected joint is hot, red and swollen and excruciatingly painful and tender. Recurrent acute attacks are followed by progressive destruction of cartilage and bone erosion – chronic gout. The other manifestations include urate urolithiasis and chronic urate nephropathy.

Interval (or) Intercritical Gout

It describes the period between attacks of acute arthritis when the individual has no joint complaints.

Chronic (or) Tophaceous Gout

Characterised by persistent polyarticular low grade pain with acute or sub acute inflammation. During this stage, tophi become apparent on physical examination.

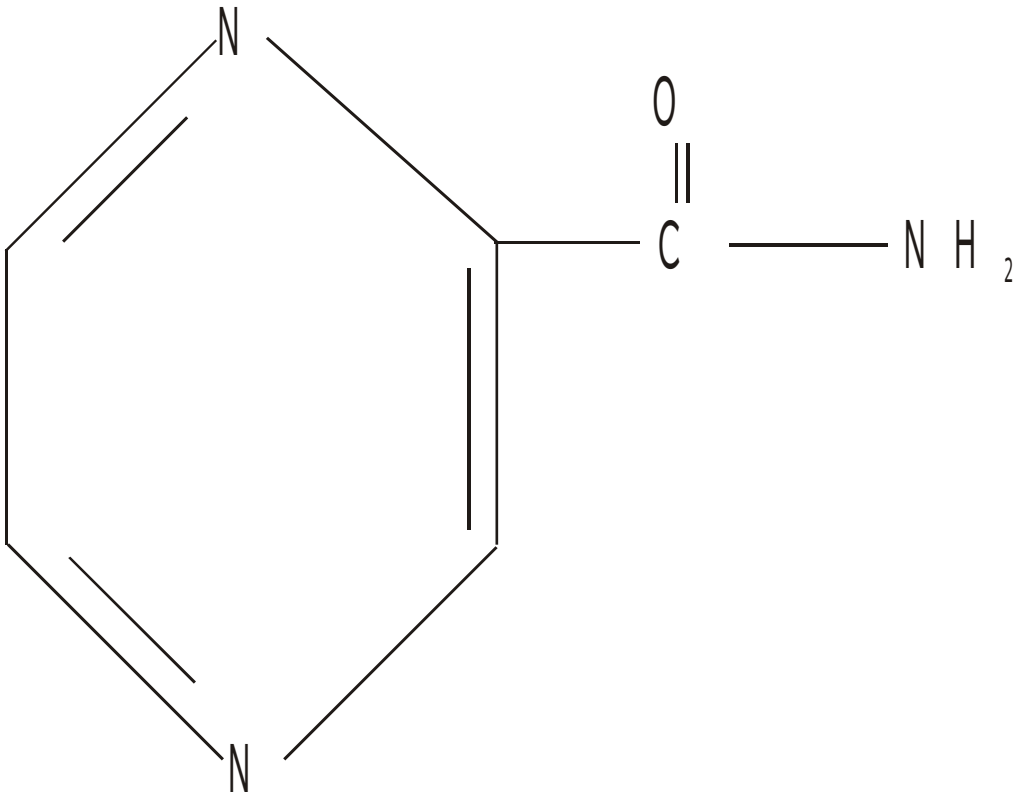
MECHANISM OF HYPERURICEMIA AND ARTHRALGIA

Mechanism of Action of Pyrazinamide

Pyrazinamide is a synthetic analogue of Nicotinamide – Pyrazinoic acid amide. The exact mechanism of the antimycobacterial action of Pyrazinamide (PZA) is not completely known. Early experimental studies showed that the activity of PZA varied with the degree of acidity of the environment.

PZA is believed to act specifically on intracellular organism partially inhibited by the acid condition of the macrophages. The current hypothesis regarding the antituberculosis action of PZA is as follows: First, in the acidic environment of the host phago lysosomes, the tubercle bacilli produce an enzyme, pyrazinamidase, that converts PZA to pyrazinoic acid (POA). In vitro, POA is inhibitory to tubercle bacilli, the degree of inhibition proportional to its concentration and a decrease in pH. POA unlike its parent compound PZA, does not seem to penetrate the membrane of the macrophage readily, Second, the POA that is produced accumulates in the phagolysosomes, thereby lowering the microenvironmental pH sufficiently to be toxic to tubercle bacilli.

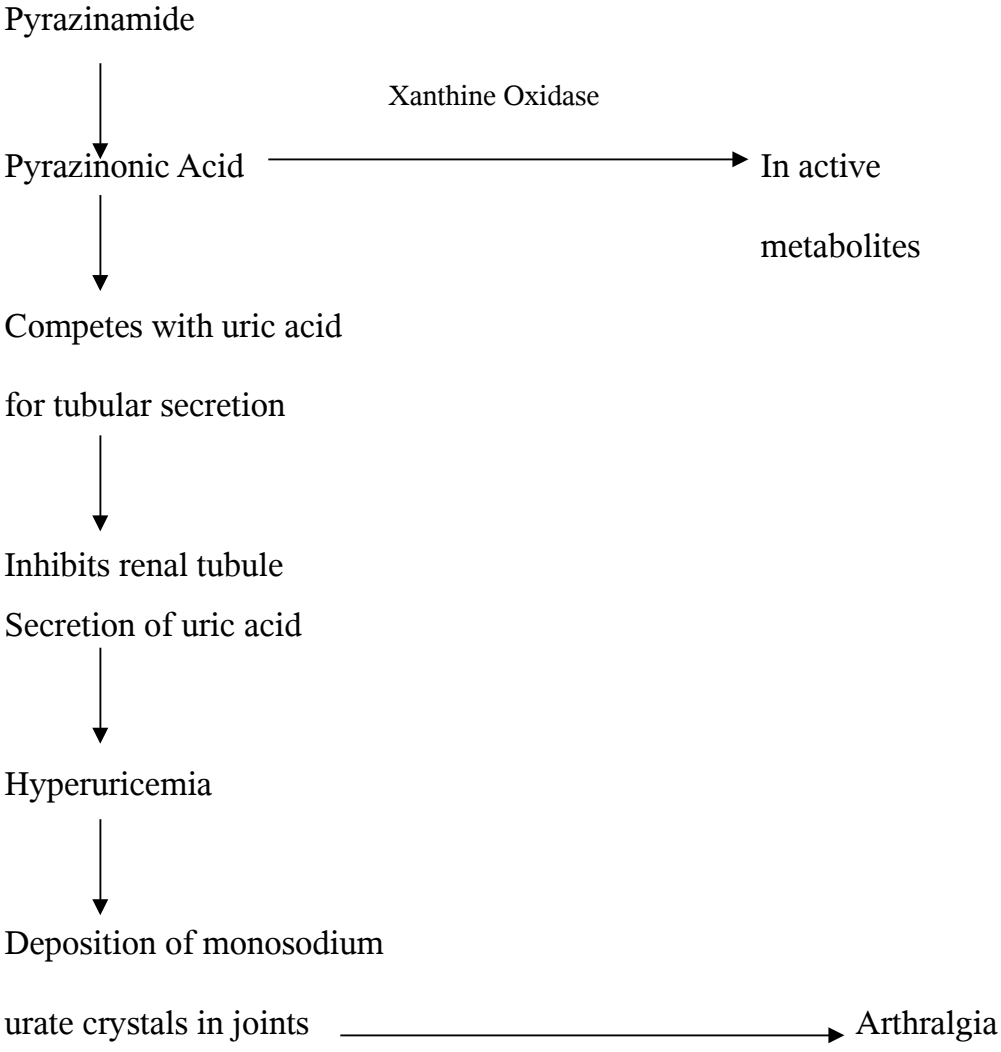
STRUCTURE OF PYRAZINAMIDE



Third, at the same time, mycobacterial metabolism produces ammonia which can increase intracellular pH, and neutralizes the acidity of POA to a certain extent, thereby decreasing the effectiveness of PZA.

MECHANISM OF PYRAZINAMIDE

INDUCED HYPERURICEMIA & ARTHRALGIA



Crowle study suggested that although low pH is probably associated

with the effectiveness of PZA. Crowle study suggested that although low pH is probably more a consequence of bacterial more a consequence of bacterial than of host cell activity. The minimal inhibitory concentration (MIC) of PZA for Mycobacterium tuberculosis on 7H 10 agar medium at pH 5.5 was shown to be 18 micro gram/ml. PZA susceptibility of a given strain of tuberculosis correlates with the pyrazinamidase activity. Susceptible strains have a high level of pyrazinamidase activity and resistant strains a reduced level of activity. This is the principle behind the in vitro PZA susceptibility testing currently used.

PZA is rapidly absorbed from the gastrointestinal tract. No evidence of the drug is detectable in the patient's faeces, which suggests that the absorption is virtually complete. The drug is distributed widely in the body. It is found in the cerebrospinal fluid in the same concentration as that in the serum of patients with tuberculous meningits. The serum half-life of PZA is 9 to 10 hours. The drug is excreated in the urine, 40 percent as pyrazinoic acid and 3 percent as unchanged PZA.

Mechanism of Hyperuricemia and Arthralgia

The exact mechanism of pyrazinamide induced hyperuricemia remains to be elucidated. The sequence of events in the causation of hyperuricemia and arthralgia in patients on pyrazinamide is depicted above.

Pyrazinamide is converted to pyrazinoic acid by hepatic deaminidase which is further hydroxylated to 5 – hydroxy pyrazinoic acid by xanthine oxidase. Pyrazinoic acid is supposed to be the active metabolism in man. Urate, the end product of purine metabolism is excreted by glomerular filtration and subsequent reabsorption in proximal tubule. The serum uric acid concentration is greatly dependent upon the rate of renal clearance of uric acid which is dependent upon the distal tubular secretion of uric acid that is almost totally inhibited by pyrazinoic acid. Pyrazinoic acid may also increase proximal reabsorption of filtered uric acid. As a result, serum uric acid concentration increases leading to deposition of monosodium urate crystals in the joints. This being the probable mechanism of action of pyrazinamide, allopurinol is not advised in the management of arthralgia since it being a xanthine oxidase inhibitor will increase the concentration of pyrazinoic acid.

MATERIALS AND METHODS

This study was carried out in patients attending the Thoracic Medicine, clinic, Govt. Rajaji Hospital Madurai from January 2008 to September 2008. Hundred and Fifty patients diagnosed to have Tuberculosis, both pulmonary and extrapulmonary were taken up for the study. This included sputum positive and sputum negative pulmonary tuberculosis patients. Patients with pleural effusion and lymphadenopathy of tuberculous etiology were also part of the study. Serum Uric Acid levels were estimated for all the patients by phosphotungstate method before treatment and at the end two months.

Procedure for estimating serum Uric Acid by Phosphotungstate method

Principle : Uric Acid, in alkaline medium reduces phosphotungstic acid into " Tungsten Blue", a blue coloured complex, which is measured colorimetrically.

Preparation of standard solution

50ml of distilled water is taken and 0.5ml of stock Uric Acid standard is added and mixed will. All other reagents are ready for use 3 ml is taken from this and to this 1 ml of sodium carbonate and 1 ml of phosphotungstate are added. After waiting for 15 minutes, reading is noted on the colorimeter.

Deproteinisation of the sample : Step A

I ml of serum is taken in a centrifuge tube, 8 ml of distilled water is added followed by 0.5ml of 2/3 N sulphuric acid and 0.5 ml of 10% W/v sodium tungstate wait for ten minutes. Then it is centrifuged for ten minutes till white precipitate completely separates.

Colour Development : Step B

3ml of the above supernatant liquid is taken and to this 1 ml of 14% W/v sodium carbonate and 1 ml of phosphotungstate are added, mixed well and kept for fifteen minutes in dark. The reading is then taken colorimetrically.

Calculation of serum Uric Acid in mg/100 ml

$$= \frac{\text{O.D test} - \text{O.D blank}}{\text{O.D std} - \text{O.D. Blank}} \times 10$$

Normal Values

Men : 25 – 7 mg/ 100 ml

Women : 1.5 – 6 mg/100 ml

1. Serum should be free from any hemolysis.
2. Use clean and dry glassware.
3. Bring all the solution to room temperature before use.

4. Prepare a blank and standard for each series of determinations.
5. Mark the test tubes properly as Blank (B), Standard (S) and Test (T) before proceeding for estimation.

STUDY DESIGN

Criteria for Inclusion

Patients aged 12 years and above of both sexes who fall into the following category were taken up for the study.

a. Newly diagnosed cases of pulmonary tuberculosis as evidenced by sputum smear for AFB positivity and those who were smear negative but had radiological lesion.
b. Cases of extrapulmonary Tuberculosis as evidenced by appropriate investigations also were a part of the study.

Criteria for exclusion:

Patients who were known to have

1. History of prior arthropathy
2. Prior ATT
3. Hypertension
4. Renal insufficiency
5. Any other medication
6. H/O chronic alcohol intake.

were excluded from the study.

The patients were divided into three groups depending on the type of

treatment they received. All sputum positive patients received IN, Rifampicin, Pyrazinamide and Ethambutol on a daily basis for 2 months followed by INH and rifampicin thrice weekly for 4 months ($2HREZ/4H_3R_3$).

Sputum negative patient and those with extrapulmonary tuberculosis received INH, Rifampicin, Pyrazinamide daily for two months followed by inh and rifampicin twice weekly for 4 months ($2\ HRZ\ /\ 4\ H_3\ R_3$).

Serum uric acid levels were estimated for all these patients before starting treatment and the end of 2 months.

Serum uric acid levels were estimated for all the patients before the start of treatment and at the end of 2 months.

The order investigations done were

1. X-ray chest PA view
2. Urine – albumin

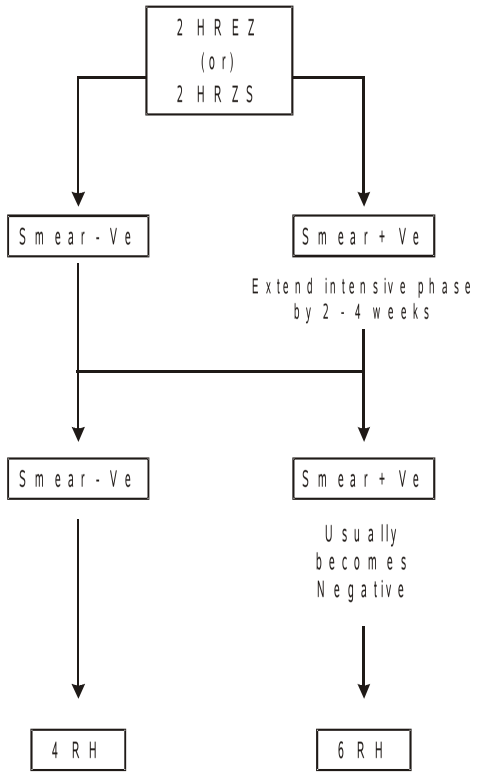
   Sugar

Revised National Tuberculosis Control Program (RNTCP)

TB treatment	TB Patients	Intensive Phase	Continuation Phase
Category I	- New smear – Positive - New smear – Negative (extensive parenchymal involvement) - Extra pulmonary (severe form)	2 HREZ or 2 HRZS	4 HR or 6 HE (if resistance to R is suspected)
Category II	Smear Positive - Relapse - Failure - Treatment after default	2 HREZS + 1 HREZ	5 HRE
Category III	New smear negative (milder form) Extra pulmonary (milder form)	2 HRZ	4 HR (or) 6 HE (if Resistance to R is suspected)

TUBERCULOSIS ALGORITHM

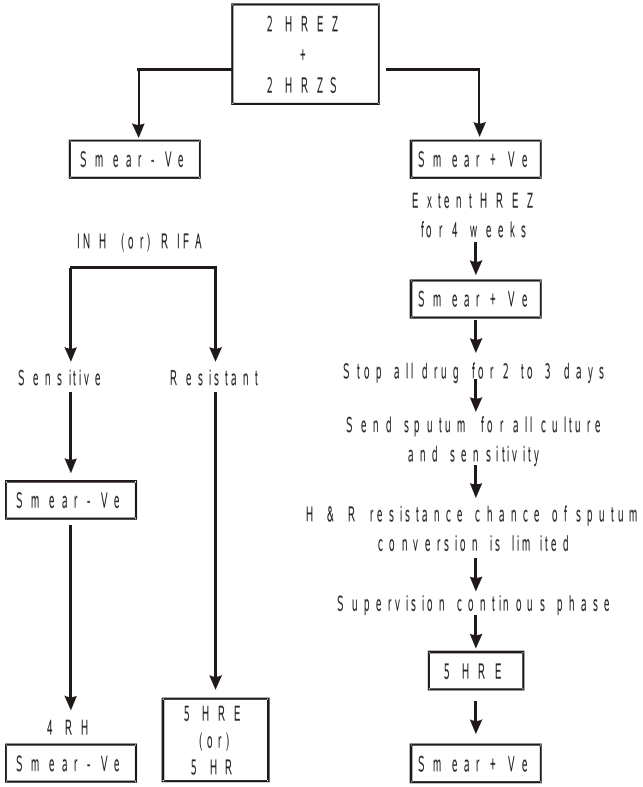
Category - I



Cured

Category - II

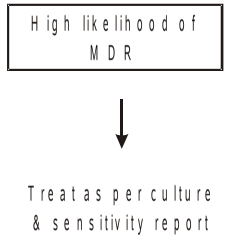
- Suspected INH & /or SM Resistant.
- High risk for MDR.
- Require supervised Prescription till Sputum becomes negative send pre - treatment sputum to culture and sensitivity.



Chronic Case

Category - III

Category - IV



RESULTS

A. CHARACTERISTICS OF CASES STUDIED

Table 1

Age distribution

Age in years	Cases	
	No.	%
Less than 20	10	6.7
20-29	33	22
30-39	27	18
40-49	28	18.7
50-59	28	18.7
60 & above	24	16
Total	150	100
Range	14 – 74 years	
Mean	41.4 years	
S.D.	15.7 years	

Age of the cases included in the study ranged from 14 years to 74 years. 46.7 % of cases were less than 40 years and 53.3% were above 40 years.

Mean age of the group was 41.4 years and standard deviation 15.7 years.

Table 2

Sex

Sex	Cases	
	No.	%
Males	96	64
Females	54	36

Men outnumbered women in the cases studied. 64 % of them were men whereas only 36% were women.

Table 3

Weight (in Kgs)

Weight (in Kgs)	Cases	
	No.	%
Upto 33 kgs	13	8.7
33 – 50 kgs	65	43.3
> 50 kgs	72	48
Range	25-67 kgs	
Mean	49.4 kgs	
S.D.	11.3 kgs	

Mean weight of the cases studied was 49.4 kgs. The minimum weight was 20 kgs and the maximum 67 kgs. Nearly half (48%) of the patients weighed 50 kgs and more.

Table 4

Regimen

Regimen	Cases	
	No.	%
HREZ	80	53.3
HRZ	70	46.7

53.3 % of the patients received HREZ regimen and 46.7% received HRZ regimen.

Table 5

Regularity of treatment

Regimen	Continued		Discontinued	
	No.	%	No.	%
HREZ (80)	66	82.5	14	17.5
HRZ (70)	58	82.9	12	17.1
Total	124	82.7	26	17.3

Out of the 80 cases receiving HREZ regimen, 14 cases discontinued treatment (17.5). Among the 70 cases who were put on HRZ regimen, an equal percentage (17.1%) discontinued. Thus a total of 26 patients (17.3) have failed to receive the full treatment.

Table 6

Serum Uric Acid

Serum Uric Acid	Range	Mean	S.D.
Before treatment	1 – 5.7	3.23	1.2
After treatment	3.3 – 12.6	6.8	1.37
Increase	0 – 8.4	3.73	1.5

Serum acid levels of the patients before treatment was 3.23 $\pm$ 1.2 and after treatment 6.8 $\pm$ 1.37.

There was an increase of 3.73 $\pm$ 1.5 at the end of the two months treatment.

CHANGES IN SERUM URIC ACID LEVELS

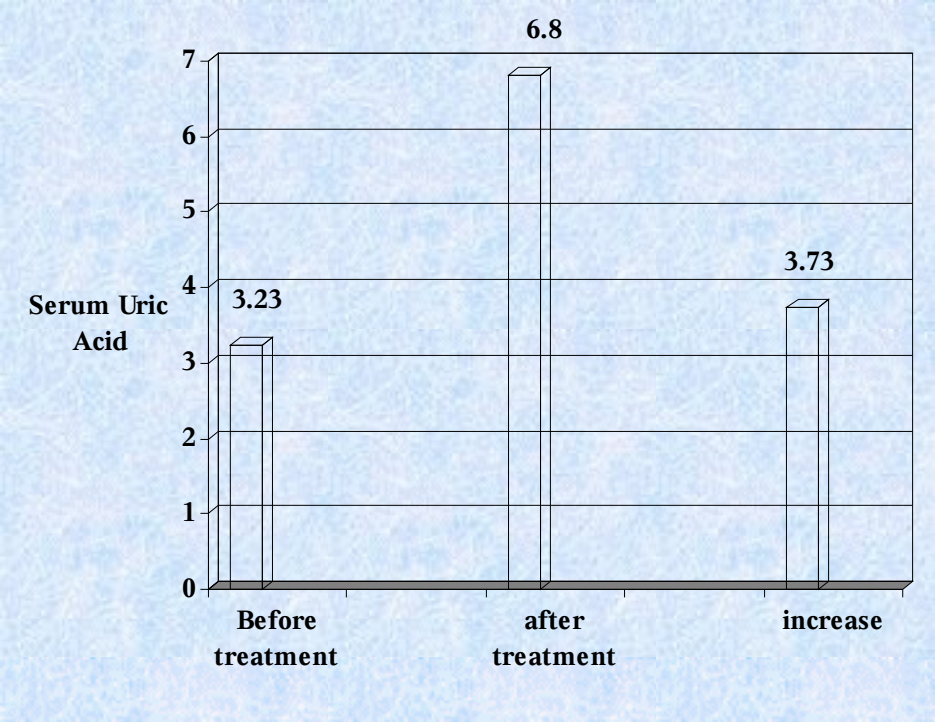


Table 7

Age distribution of patients in the two regimen

Age group	Regimen			
	HREZ		HRZ	
	No.	%	No.	%
Less than 20(10)	4	40	6	60
20-29 (33)	15	45.5	18	54.5
30-39 (27)	17	63	10	37
40-49 (28)	12	42.9	16	57.1
50-59 (28)	19	67.9	9	32.1
60 & above (24)	13	54.2	11	45.8
Total (150)	80	100	70	100
Range	14 – 70 years		14 – 74 years	
Mean	42.6 years		40.1	
S.D.	15.3 years		16.1	
'p'	0.2778 Not significant			

The mean age of patients receiving HREZ was 42.6 years and those receiving HRZ was 40.1 years. The difference was not statistically significant ($p > 0.05$)

Table 8

Sex distribution of patients in the two regimen

Sex	Regimen			
	HREZ		HRZ	
	No.	%	No.	%
Males (96)	51	53.1	45	46.9
Females(54)	29	53.7	25	46.3
Total	80	100	70	100
'p'	0.9185 Not significant			

The sex composition of the patients receiving the two different types of treatment was nearly identical and there was no statistically significant difference.

Table 9

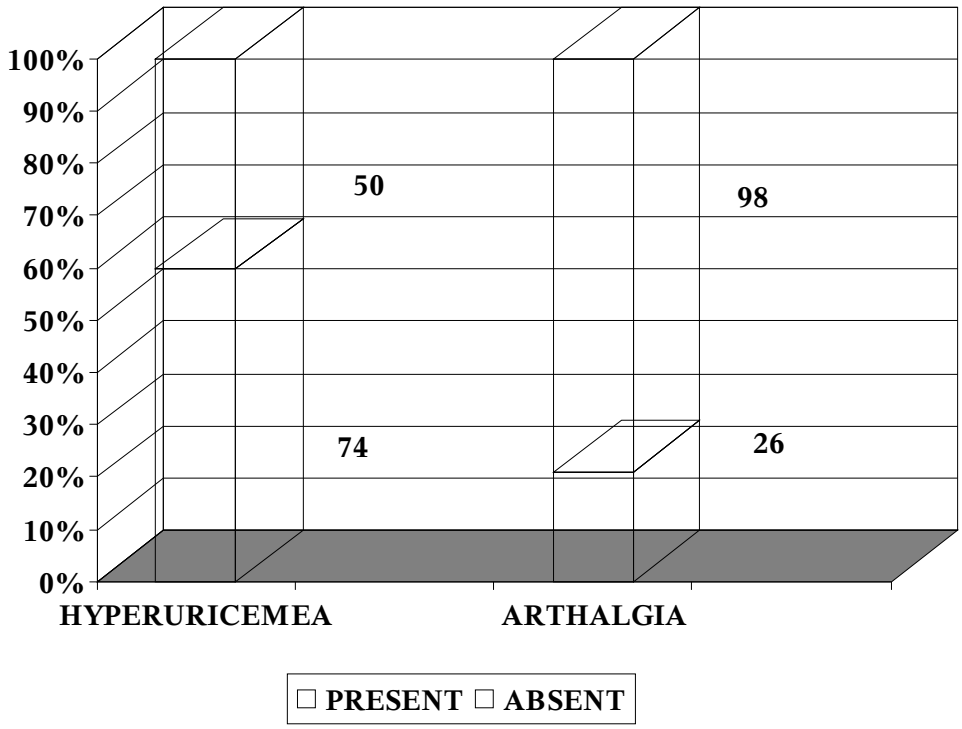
Incidence of Hyperuricemeia and Arthralgia in the two regimen

Complication	Yes		No	
	No.	%	No.	%
Hyperuricemeia	74	59.7	50	40.3
Arthralgia	26	21	98	79

* 26 patients discontinued treatment

Out of the 124 cases continuing treatment at the end of 2 months, 74 (59.7) had hyperuricemeia and 26 (21%) had arthralgia.

INCIDENCE OF HYPERURICEMIA & ARTHRALGIA



B. RELATIONSHIP BETWEEN VARIOUS PARAMETERS AND INCREASE IN SERUM URIC ACID LEVELS

Table 10

Age and increase in Serum Uric Acid

Age group	Serum Uric Acid					
	Before treatment		After treatment		Increase	
	Mean	S.D.	Mean	S.D	Mean	S.D.
Less than 20	2.98	1.02	7.35	0.41	4.37	1.33
20-29	3.32	1.25	7.17	0.78	4.02	1.25
30-39	3.24	1.25	7.14	1.08	4.23	1.08
40-49	3.47	1.33	7.01	1.56	3.75	1.81
50-59	3.39	1.2	6.6	1.34	3.3	1.8
60 & above	2.77	0.96	5.67	1.05	2.89	1.19
'P'	0.4589 Not significant		**0.0001 Significant**		**0.007 Significant**	

Before treatment there was no significant difference in serum uric acid levels. After the treatment there is decrease in serum uric acid levels and the difference is also statistically significant. Similarly there is statistically significant relationship between age and increase in serum uric acid levels ($p = 0.007$).The increase is more in the younger age groups.

AGE AND SERUM URIC ACID

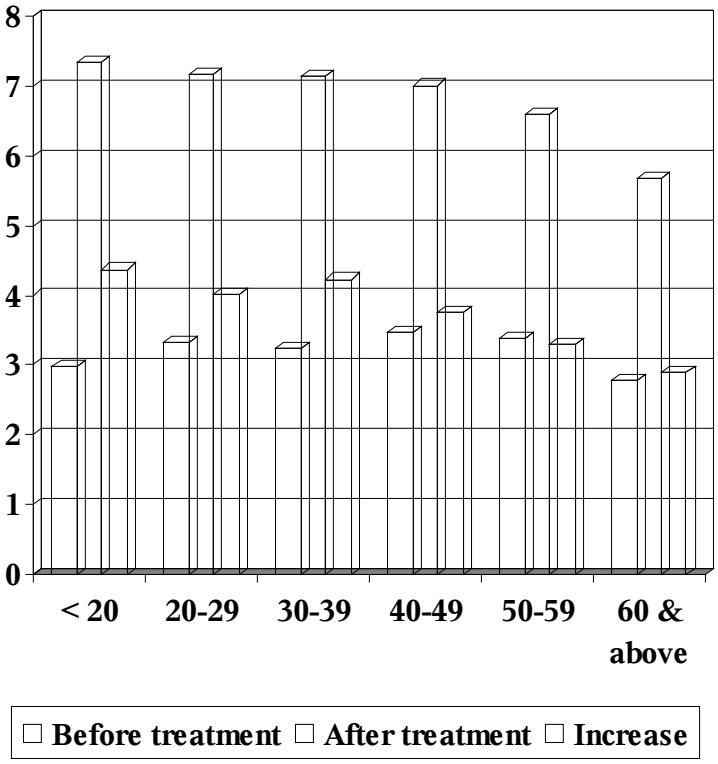


Table 11

Sex and increase in Serum Uric Acid

Sex	Serum Uric Acid					
	Before treatment		**After treatment**		**Increase**	
	Mean	S.D.	Mean	S.D	Mean	S.D.
Males	3.41	1.15	6.85	1.39	3.64	1.51
Females	2.92	1.24	6.71	1.34	3.88	1.47
'p'	0.0267 Significant		0.8474 Not significant		0.2178 Not significant	

There is no statistically significant difference in the serum uric acid levels after treatment and increase in serum uric acid levels between males and females.

Table 12

Drug regimen and increase in Serum Uric Acid

Drug regimen	Serum Uric Acid					
	Before treatment		After treatment		Increase	
	Mean	S.D.	Mean	S.D	Mean	S.D.
HREZ	3.24	1.06	6.99	1.18	3.81	1.58
HRZ	3.23	1.35	6.58	1.53	3.63	1.39
'P'	0.612 Not significant		0.1144 Not significant		0.6181 Not significant	

There is no significant relationship the serum uric acid levels and the drug regimen ('p' = 0.612).

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C. RELATIONSHIP BETWEEN VARIOUS PARAMETERS AND INCIDENCE OF HYPERURICEMEIA

Table 13

Age and incidence of hyperuricemia

Age group	Incidence of hyperuricemia			
	Yes		No	
Less than 20(10)	10	100	-	-
20-29 (27)	25	92.6	2	7.4
30-39 (23)	19	82.6	4	17.4
40-49 (22)	12	54.5	10	45.5
50-59 (21)	6	28.6	15	71.4
60 & above (21)	2	9.5	19	90.5
Mean S.D.	32.7 years 12.7 years		53.6 years 12.4 years	
'p'	**0.0001** **Significant**			

As age increases, incidence of hyperuricemia decreases. There exists statistically significant relationship between age of the patient and incidence of hyperuricemia in TB patients. (p = 0.0001).

AGE AND HYPERURICEMIA

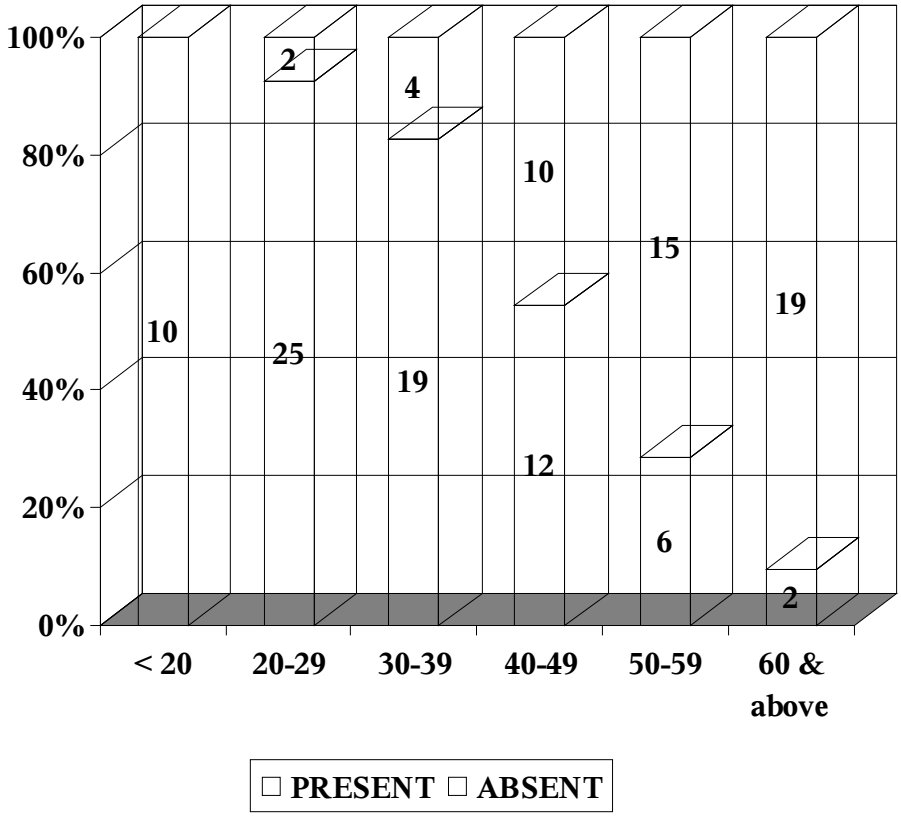

Table 14

Sex and incidence of hyperuricemia

Sex	Incidence of hyperuricemia			
	Yes		No	
	No	%	No	%
Males (79)	46	58.2	33	41.8
Females(45)	28	62.2	17	37.8
'p'	0.8059 Not significant			

There is no significant difference in the incidence of hyperuricemia among males and females.

Table 15

Drug regimen and incidence of hyperuricemia

Drug regimen	Incidence of hyperuricemia			
	Yes		No	
	No	%	No	%
HREZ (66)	42	63.6	24	36.4
HRZ (58)	32	55.2	26	44.8
'p'	0.4382 Not significant			

Among the TB patients receiving HREZ and HRZ regimens, there is no significant difference in the incidence of hyperuricemia

D. RELATIONSHIP BETWEEN VARIOUS PARAMETERS AND INCIDENCE OF ARTHALGIA

Table 16

Age and incidence of Arthralgia

Age group	Incidence of Arthralgia			
	Yes		No	
Less than 20(10)	2	20	8	80
20-29 (27)	7	25.9	20	74.1
30-39 (23)	7	30.4	16	69.6
40-49 (22)	6	27.3	16	72.7
50-59 (21)	1	4.8	20	95.2
60 & above (21)	3	14.3	18	85.7
Mean S.D.	36.6 years 14.0 years		42.4 years 16.6 years	
'p'	0.1248 Not significant			

Age of the patient and incidence of arthralgia are not significantly related ('p' = 0.1248).

Table 17

Sex and incidence of Arthralgia

Sex	Incidence of Arthralgia			
	Yes		No	
	No	%	No	%
Males (79)	14	17.7	65	82.3
Females (55)	12	26.7	33	73.3
'p'	0.3435 Not significant			

Incidence of arthralgia has got no significant relationship with sex of the patient.

Table 18

Drug regimen and incidence of Arthralgia

Drug regimen	Incidence of Arthralgia			
	Yes		No	
	No	%	No	%
HREZ (66)	17	25.8	49	74.2
HRZ (58)	9	15.5	49	84.5
'p'	0.2393 Not significant			

Drug regimen and arthralgia do not have statistically significant relationship ('p' = 0.2392).

Table 19

Incidence of hyperuricemia and Arthralgia

Hyperuricemia	**Arthralgia**			
	Yes		**No**	
	No	%	No	%
Yes (74)	20	27	54	73
No (50)	6	12	44	88
‘p’	0.0732			

Incidence of hyperuricemia and arthralgia are not related. ($p > 0.05$)

DISCUSSION

The incidence of hyperuricemia and arthralgia observed in the study in the pyrazinamide containing regimens were 59.7% and 21% and this result is similar to those observed by other workers. The overall incidence of arthralgia in the various studies varies from nil (Zierski and Bek 1980) to as high as 67% has been reported by Sharma et. al. 1980.

Studies from Tuberculosis Research Centre (1983-84), Tripathi et. al. 1979, Sharma and Jain 1980-83 have speculated on the possible Rifampicin group and 66% of the one hundred and seventy nine patients in the non-rifampicin group. The same workers have reported an incidence 24% of three hundred and eighty patients in the Rifampicin group and 46% in the non-rifampicin group.

Tolerance of Pyrazinamide in Short Course Chemotheraphy for pulmonary tuberculosis in children (up to 15years). This prospective study from Department of pediatrics, hospital infantal la paz, Madrid, Spain. (1985-1995). Study showed increased serum uric acid in 92.2% of the children (total of 114 children) and significant fell again 1 month after Pyrazinamide stopped. There was no sign of arthralgia.

Year	Worker	Hyperuricemia	Arthralgia
1981	Sharma et. al.	43%	16%
1983	Sharma et. al.	79%	19%
1978	Iyer & Srinivasan	70%	67%
1961	Vely et. al.	58%	24%
1983	TRC (Tuberculosis Research Centre	66%	46% (Non-Rifampicin Group)
1983	TRC	69%	24% (Rifampicin group)
1981	Mehotra et. al.	72%	10%
1980	TB Association of India	70%	13%
1976	Hongkong TB Association / BMRC	59%	7%
1981	Singapore / BMRC	49%	1%
1980	Zierski & Bed	60%	0%

The role Rifampicin in Pyrazinamide induced arthralgia has been studied at Tuberculosis Research Centre, Chennai.

Renal excretion of uric acid is suppressed by Pyrazinamide being less than 40% at five hours. The excretion of uric acid increases thereafter and returns to pretreatment values at 24 hours. The serum concentration shows little or no change suggesting that the serum is probably saturated at this concentration and any further uric acid must be deposited in the joints or eliminated by uricolysis.

The sustained level of uric acid increases at 24 hours after drug administration despite the urinary excretion returning to pre-treatment levels may be due to the dynamic equilibrium between the deposited uric acid and the serum uric acid by mobilizing uric acid from tissues and this could be responsible for the lack of association between arthralgia and serum uric acid concentration.

The uricosuric effect of rifampicin could be due to the inhibition of tubular reabsorption of filtered uric acid at a post-secretary absorptive site, an effect similar to uricosuric agents like salicylate and probenecid. Moreover Rifampicin is a known inducer of hepatic microsomal enzymes and this could mean a greater activity of pyrazinamide deamidase. In addition to the uricosuric effect, rifampicin also increases the renal elimination of pyrazinoic acid, which is the major metabolite responsible for the inhibition of secretion of uric acid from the distal tubule.

In the present study, the incidence of hyperuricemia and arthralgia with pyrazinamide therapy was 59.7% (74 out of 124) and 21% (28 out of 124) respectively. The onset of arthralgia was within 15 days of starting therapy in the majority of cases. However, none of the patients had to be discontinue treatment because of arthralgia. The patients continued the normal activities receiving symptomatic treatment with tablet Ibuprufen 400mg three times a

day. In this study all the arthralgic patients were hyperuricemic. However only one third of hyperuricemics had arthralgia indicating that hyperuricemia and arthralgia were not synonymous. In other words, the hyperuricemia associated with pyrazinamide was mostly asymptomatic. It was also noticed that there was a statistically significant reduction in the incidence of hyperuricemia with advancing age.

Further work on this association is indicated. There was no correlation between the degree of hyperuricemia and severity of arthralgia symptoms. There was no incidence of acute gout in our study. There was no relationship between the dosage of Pyrazinamide and development of hyperuricemia of arthralgia. Hyperuricemia and arthralgia had no statistically significant association with sex.

Multiple joint involvement was seen in 4 cases. There was no involvement of small joints in our study. In contrast to gout, involving small joints like toes is usual and simultaneous involvement of two or more joints is uncommon (Graham & Scott 1970).

There is only circumstantial evidence to implicate hyperuricemia in pyrazinamide arthropathy. As pointed out by Horsfall et al., on account of difference in the types of joints involved between pyrazinamide arthropathy

and gout it is possible that different mechanisms may be operative in the two conditions.

The detection of arthralgia was purely a subjective phenomenon. No leading questions were asked and any spontaneous complaint was noted followed by examination of the affected joint. This could depend on various factors like patients willingness to be forthcoming with their problem and awareness of the patient.

In contrast to the weight bearing joint like knee which was involved in our study, in the Hongkong / BMRC study the commonly involved joint was shoulder (Hors fall et al. 1972).

Finally as far as the incidence of arthralgia is concerned it is unlikely that subjective errors in the diagnosis of arthralgia would entirely account for the large geographical variation observed. Whether this is due to genetic, nutritional or some other factor remains to be determined. The susceptibility to arthralgia might depend on factors like concentration of urate binding protein in individuals.

CONCLUSION

FROM THE STUDY WE ARRIVED AT THE FOLLOWING CONCLUSIONS.

1. Pyrazinamide therapy is associated with hyperuricemia

In our study out of 74 out of 124 (59.7%) patients had hyperuricemia. Increase in serum uric acid levels has significant relationship with age but not with sex and regimen.

2. Hyperuricemia and arthralgia are not synonymous

In our study out of 124 patients 28 (21%) were only arthraligic, out of 74 patients with hyperuricemia. Only 20 (27%) had arthralgic. Age, Sex and dose of drug not related to arthralgia.

3. Pyrazinamide induced hyperuricemia is not related to sex or dosage. But is related to age which is statistically significant

In our study compared to older age group, younger age is more susceptible to hyperuricemia. In patients less than 40 years, the incidence is 80 to 100% and in patients more than 40 years old it was only 10 to 50%.

APPENDIX

PROFORMA

Serum uric acid estimation in patients receiving regimen containing Pyrazinamide

Name	:	Age	:	Sex	:
Address	:	Occupation	:	Op No	:
Income	:	Index No	:	Regimen	:
Complaints	:	Duration	:		
Weight	:				

Past History

a. H/O prior antituberculosis treatment.

b. History of previous joint pain.

c. History of gout.

d. History of hypertension

e. History of renal insufficiency.

f. History of chronic intake of any medications.

g. History of alcohol intake / smoking

General Examination

Systemic examination	:	
Respiratory system	:	
Cardiovascular system	:	
Central nervous system	:	
Abdomen	:	

Examination of Joints

1. Joint/Joints involved	:	Present / Absent
2. Pain	:	Present / Absent
3. Limitation of movement	:	Present / Absent
4. Tenderness	:	Present / Absent
5. Joint swelling	:	Present / Absent
6. Effusion and discolouration of skin	:	Present / Absent

Investigations

a. X-Ray Chest PA view – 0, 2nd month
b. Sputum smear for AFB – 0,2nd month
c. Urine for Albumin/Sugar/Deposit.
d. Mantoux
e. Pleural fluid analysis.
f. Serum Uric acid –
    1. To estimate before treatment started.
    2. To estimate every 15 days during intensive phase.
    3. To estimate at the end of intensive phase.
g. Blood, TC, DC, ESR, Hb%

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MASTER CHART

S. No	Name	Age	Sex	Weight	Regimen	Uric acid		Arthralgia
						Before treatment	After treatment.	
1	Perumayee	18	F	28	HREZ	1.2	8.1	1
2	Ramasamy	52	M	63	HREZ	2	5.4	2
3	Arumugam	63	F	60	HRZ	2.5	3.4	2
4	Chitra	54	F	61	HRZ	4.2	8	2
5	Ganapathy	19	M	35	HRZ	3.6	7	2
6	Sivanandi	53	M	64	HREZ	4.2	12.6	2
7	Valli	20	F	25	HRZ	3	6.5	2
8	Ramasamy	20	M	35	HREZ	2.8		2
9	Muthupillai	22	F	34	HRZ	4.4	7.1	2
10	Ayyanar	26	M	50	HRZ	2	5	2
11	Srinivasan	17	M	28	HREZ	1.2	7.6	1
12	Muthu	48	F	64	HRZ	2	4.2	2
13	Kirupanandham	65	M	59	HRZ	3.7	7	2
14	Thangavelu	62	M	58	HREZ	5.1	7.1	1
15	P aramasamy	23	M	40	HRZ	5	6.6	2
16	Malaiyappan	45	M	51	HREZ	4.2		2
17	Thangam	32	M	50	HREZ	4.2	8.2	1
18	Petchiammmal	43	F	48	HREZ	2	9.7	2
19	Mookammal	33	F	42	HRZ	2.1	8	1
20	Andammel	26	F	42	HRZ	2.1	6.6	2
21	Vasanthi	18	F	28	HREZ	3.9	6.9	2
22	Chinnnaadaikkan	44	M	62	HRZ	5.1		2
23	Senthikani	26	F	32	HRZ	1.8	6.1	2
24	Rameshbabu	27	M	40	HRZ	4.8	9.1	2
25	Ramasamy	56	M	52	HREZ	3	4.4	2
26	Azhagu	22	M	45	HRZ	2.6	3.6	1
27	Ramar	14	M	25	HREZ	2.8	5.6	2
28	Mangaiyarkarasi	50	F	65	HREZ	4.9		2
29	Chinnammal	24	F	40	HRZ	4.4	6.7	2
30	Ganesan	57	M	65	HREZ	2.8	4.4	2
31	Karuppaiya	38	M	50	HREZ	1.8	4.8	1
32	Mayandi	39	M	48	HRZ	4.9		2
33	Kazhuvayee	48	F	64	HRZ	5.6	10.2	1
34	Muthu	50	M	58	HREZ	4.7	6.9	2
35	Ganga	20	F	35	HRZ	3.1	5.6	2
36	Azhagu	67	M	62	HREZ	2.5	7.2	2
37	Rakku	33	F	62	HRZ	5.1		2
38	Muthup andi	74	F	67	HRZ	1.6	2.8	2
39	Ramu	32	M	46	HREZ	3.1	6.4	2
40	Jeyaprakash	31	M	45	HREZ	2.8	6.4	2
41	Nagaraj	30	M	45	HREZ	4	6.6	2
42	Saravansalen	30	M	45	HREZ	3.8	7.4	2

S. No	Name	Age	Sex	Weight	Regimen	Uric acid		Arthralgia
						Before treatment	After treatment.	
43	Arunkumar	48	M	60	HRZ	1.8	8	2
44	Manickam	62	M	65	HREZ	2.6		2
45	Chellakannu	44	M	48	HRZ	1.9	7.8	1
46	Muthu	53	F	48	HREZ	3	6	2
47	Manimegalai	37	F	45	HREZ	3.2	4.8	2
48	Sonaimuthu	49	M	52	HRZ	4.2	4.8	2
49	Vanitha	55	F	62	HREZ	2.9		2
50	Kanthan	16	M	34	HRZ	3.8	5.2	2
51	Govindhan	58	M	60	HRZ	4	9.6	2
52	Ravichandran	25	M	38	HREZ	4.2	6.6	2
53	Muthupechi	57	F	62	HREZ	2.3		2
54	Rajendran	33	M	45	HREZ	3.8	9.4	1
55	Paulpandy	44	M	45	HRZ	2.7	4.7	2
56	Kalimuthu	58	M	58	HRZ	2	5.3	2
57	Paunraj	41	M	50	HREZ	4.1	7.2	2
58	Sekar	50	M	62	HREZ	5.4		2
59	Ramesh	33	M	52	HRZ	2	4	2
60	Perumal	48	M	52	HREZ	5.1	7.7	2
61	Kazhuvayee	55	F	50	HRZ	1	3.1	2
62	Muniyan	65	M	60	HRZ	2.2	4.7	1
63	Ganesh	40	M	55	HRZ	2.3	3.7	2
64	Selvi	40	F	42	HREZ	2.6	7.4	2
65	Avudaiachi	50	F	45	HRZ	2.5		2
66	Muthu	53	M	55	HRZ	2.3	4.6	2
67	Vairavan	62	M	65	HRZ	3	2.3	2
68	Alagammel	62	F	64	HREZ	3.1	7.4	2
69	Sumathi	40	F	40	HREZ	4.1	6.5	2
70	Thangaraj	28	M	38	HRZ	5.5		2
71	Murugan	61	M	60	HRZ	3	4	2
72	Paulkanna	64	M	60	HREZ	2	4.5	2
73	Seeniammal	70	F	58	HREZ	2.8	6	2
74	Sivagami	20	F	28	HREZ	2.2	6.8	1
75	Raju	32	M	48	HREZ	1.7	7.3	2
76	Chinnaiya	38	M	58	HRZ	1.2	4.1	2
77	Shenbagam	26	F	35	HREZ	4	4.4	1
78	Geetha	58	F	58	HREZ	5.6		2
79	Kaunammal	56	F	53	HREZ	3.2	6.7	2
80	Paramasivam	55	M	62	HREZ	2.2	6.2	2
81	Madhivanan	23	M	30	HREZ	2.4	8.4	2
82	Malliga	45	F	40	HREZ	2	4.7	2
83	Govindammal	62	F	62	HREZ	2.9		2
84	Subramani	24	M	40	HREZ	2.6	7.6	2
85	Kangammal	25	F	40	HREZ	1.2	4	1
86	Aadeeswari	38	F	58	HRZ	1	4.7	2
87	Perumal	46	M	64	HREZ	3.9		2
88	Sureshkumar	32	M	48	HREZ	3	6.8	2
89	Suresh	49	M	60	HREZ	4	5.4	2

S. No	Name	Age	Sex	Weight	Regimen	Uric acid		Arthralgia
						Before treatment	After treatment.	
90	Mohammed Meeran	63	M	58	HREZ	3	5.4	2
91	Angulakshmi	68	F	28	HRZ	1.5	8.2	2
92	Thirumugam	45	M	56	HREZ	2.2	5.9	2
93	Kannan	45	M	62	HRZ	2.7		2
94	Venkateshan	25	M	34	HREZ	2.8	8.6	2
95	Subbiah	32	M	48	HRZ	4.1	7.1	2
96	Mylathal	40	F	48	HREZ	5.4	4.4	1
97	Gandhimathi	26	F	40	HREZ	3.3	6.9	2
98	Veerachamy	29	M	48	HRZ	5.7		2
99	Mohan	42	M	60	HRZ	4.1	6.4	1
100	Pasumpon	29	F	42	HREZ	2.4	6.9	1
101	Sumathy	25	F	33	HRZ	2.1		2
102	Dhanalakshmi	38	F	45	HREZ	2.1	6.5	1
103	Anwar	72	M	62	HRZ	2.3	5.4	2
104	Subramanian	14	M	32	HRZ	2.8	6.4	2
105	Chinamuthu	65	M	60	HRZ	2.2	4.7	1
106	Mariappan	49	M	60	HREZ	4	5.4	2
107	Pandiyan	61	M	56	HREZ	5.1	7.1	1
108	Abdullah	31	M	41	HREZ	4	6.6	2
109	Murugan	53	M	53	HREZ	5.1	7.7	2
110	chitra	40	F	42	HREZ	2.6	7.4	2
111	devi	52	F	60	HREZ	2.3		
112	Raman	24	M	47	HRZ	2.6	3.6	1
113	Sundari	25	F	33	HRZ	2.1		
114	Seeniappan	57	M	62	HRZ	4	9.6	2
115	Sundararaj	25	M	38	HREZ	4.2	6.6	2
116	Mariyamma	50	F	65	HREZ	4.9		
117	Mariappan	45	M	51	HREZ	4.2		
118	Pandiyan	26	M	50	HRZ	2	5	2
119	Abdullah	30	M	45	HREZ	3.8	7.4	2
120	Murugan	31	M	49	HRZ	5.7		
121	Sivakumar	23	M	30	HREZ	2.4	8.4	2
122	Raji	54	F	61	HRZ	4.2	8	2
123	Stephen	20	M	42	HRZ	5	6.6	2
124	Chellamma	58	F	58	HREZ	5.6		
125	Veeranan	42	M	57	HRZ	2.3	3.7	2
126	Rani	20	F	29	HREZ	2.2	6.8	1
127	Kuppan	30	M	47	HREZ	3.8	9.4	1
128	Mangai	19	F	36	HRZ	3.1	5.6	2
129	Rajendran	41	M	50	HREZ	4.1	7.2	2
130	Kalavathy	48	F	64	HRZ	5.6	10.2	1
131	Ashok	44	M	62	HRZ	5.1		
132	Rangasamy	65	M	59	HRZ	3.7	7	2
133	Amudha	26	F	42	HRZ	2.1	6.6	2
134	Paneer Selvam	16	M	34	HRZ	3.8	5.2	2
135	Perumal	62	M	65	HRZ	3	2.3	2

S. No	Name	Age	Sex	Weight	Regimen	Uric acid		Arthralgia
						Before treatment	After treatment.	
136	Sivagami	38	F	58	HRZ	1	4.7	2
137	Shenbagam	26	F	40	HREZ	3.3	6.9	2
138	Geetha	49	F	62	HRZ	2	4.2	2
139	Chinnapayan	66	M	60	HREZ	2.5	7.2	2
140	Arumugam	58	M	60	HRZ	2.2	4.7	1
141	Manikandan	24	M	39	HRZ	5.5		
142	Karthikeyan	47	M	61	HRZ	1.8	8	2
143	Kumar	63	M	57	HRZ	3.7	7	2
144	Kangammal	40	F	48	HREZ	5.4	4.4	1
145	Aadeeswari	26	F	35	HREZ	4	4.4	1
146	Jeyaraj	50	M	62	HREZ	5.4		
147	Mylathal	53	F	48	HREZ	3	6	2
148	Muthusamy	14	M	25	HREZ	2.8	5.6	2
149	Kayakudiyan	17	M	28	HREZ	1.2	7.6	1
150	Karthik	30	M	45	HREZ	4	6.6	2